REMARKS

Claims 1 and 18 are amended to replace the terms "in need of such treatment" with "having macular degeneration." Claim 23, which is dependent on claim 1, is added to recite the administration of from about 1 mg to about 5,000 per day. Claim 24, which is dependent on claim 1, is added to recite the administration of from about 10 mg to about 2,500 per day. Claim 25, which is dependent on claim 1, is added to recite the administration of from about 100 mg to about 1,200 mg per day. Support for claims 23-25 may be found, for example, on page 26, lines 6-8 of the specification. Following entry of the new claims, claims 1-7, 18-19, and 23-25 will be pending in this application.

I. Applicant's Statement of the Substance of Interview and Response to the Examiner's Interview Summary of Record

A personal interview with Patent Examiner Zohreh A. Fay, Applicant's representative Dr. Donna Robertson-Chow, and attorneys for Applicant Yeah-Sil Moon and Dr. Robert Chang was held on February 18, 2009. Applicant appreciates the Examiner interview.

During the interview, the pending rejection under 35 U.S.C. §103 was discussed. Attorneys for Applicant explained that U.S. Patent No. 6,020,358 ("Muller"), alone or in combination with U.S. Patent No. 6,428,787 ("Tobinick") and U.S. Patent No. 6,235,756 ("D'Amato"), fails to suggest the claimed methods of using the recited compound, cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindoline-4-yl}carboxamide, for the treatment of macular degeneration.

First, attorneys for Applicant pointed out that the recited compound is not specifically disclosed as an individual species in Muller. Further, attorneys for Applicant pointed out that the genus disclosed in Muller is broad and encompasses thousands of compounds. Attorneys for Applicant pointed out that to arrive at the instant compound, one skilled in the art would have had to select specific values for at least 13 variables, each one of which is defined broadly. Attorneys for Applicant emphasized that not one of the twenty species disclosed in Muller have a cyclopropylcarboxamide substituent. Attorneys for Applicant also pointed out that the instant claims recite the use of a single specific stereoisomer, *i.e.*, *S*-isomer, and that Muller does direct one to the *S*-isomer, much less its use in macular degeneration. Attorneys for Applicant pointed out that Tobinick and D'Amato do not cure these defects. Attorneys

for Applicant submitted that Tobinick actually teaches away from the recited compound by focusing on antibodies, not a small molecule as in the instant claims.

Second, attorneys for Applicant pointed out that the cited references do not suggest the disorder recited in the method of treatment claim, *i.e.*, macular degeneration. Attorneys for Applicant pointed out that macular degeneration is disclosed among a large number of disorders in Tobinick, and none of the references would have suggested singling out macular degeneration. The Examiner appeared to agree that the cited references do not suggest the use of the recited compound for treating macular degeneration, and that Applicant's arguments support Applicant's position in the §103 rejection.

Third, attorneys for Applicant stressed that the §103 obviousness rejection also can be overcome by unexpected results of the claimed invention. Attorneys for Applicant pointed out that the previously submitted declaration from Peter H. Schafer ("Declaration") evidenced that the instant compound is effective in treating macular degeneration. Attorneys for Applicant pointed out that the observed activity was comparable to Lucentis®, which is the current "gold-standard" for the treatment of macular degeneration. Next, attorneys for Applicant stressed that the data presented in the Declaration are based on a widely accepted model used by those skilled in the art for the identification of candidates that are clinically effective in the treatment of macular degeneration. The Examiner agreed that unexpected results of the claimed invention can overcome the §103 rejection.

Applicant's arguments and evidence are discussed below and presented herewith.

II. Arguments and Response to Rejections

The Rejection Under 35 U.S.C. §103(a) Should Be Withdrawn.

On page 2 of the Office Action, the Examiner has maintained the rejection of claims 1-7, 18, and 19 under 35 U.S.C. §103(a) as being allegedly unpatentable over Muller *et al.*, U.S. Patent No. 6,020,358 ("Muller") in view of Tobinick, U.S. Patent No. 6,428,787 ("Tobinick"), and D'Amato, U.S. Patent No. 6,235,756 ("D'Amato"). Specifically, it is alleged that the instant claims are obvious because (1) Muller allegedly teaches "the use of the claimed compounds[1] as TNF alpha reducing compounds;" (2) Tobinick allegedly teaches "the use of TNF alpha blockers or antagonists for the treatment of...macular degeneration;"

[1] As the use of a single compound is claimed, Applicant assumes the term "compounds" is a typographical error.

and (3) "D'Amato teaches the use of the claimed secondary components...." Office Action, page 3. Applicant respectfully traverses this rejection.

Applicant respectfully submits that the rejection under 35 U.S.C. §103 is improper because:

(A) the Examiner fails to establish a *prima facie* case of obviousness; and

(B) even if a *prima facie* case has been established, sufficient unexpected results are provided to overcome any *prima facie* case of obviousness.

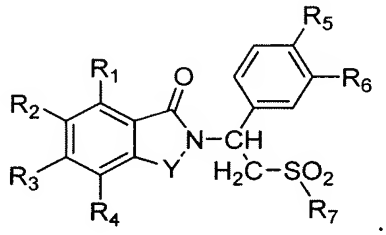
A. The Examiner fails to establish a *prima facie* case of obviousness

As discussed at the interview held on February 18, 2009, the PTO has failed to establish a *prima facie* case of obviousness. The instant claims are narrowly focused on the non-obvious use of a single isomer of a single racemate– cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindoline-4-yl}carboxamide ("instant compound") – for the treatment of a specific disorder – macular degeneration. Yet the Office Action fails to adequately explain why a person of ordinary skill in the art would have had a reason to specifically use the instant compound for treating any disorder, much less treating macular degeneration, and have a reasonable expectation of success in doing so. Such is required to establish a *prima facie* case of obviousness. *See e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d at 1342, 1360 (Fed. Cir. 2007) ("[t]he burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so.") (emphasis added, internal quotations omitted); *see also Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1090 (Fed. Cir. 2008).

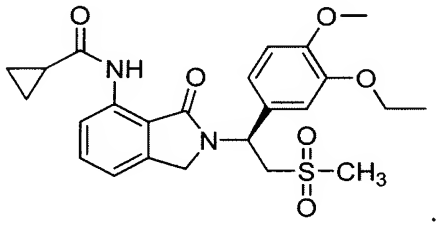
Muller does not disclose the instant racemate as a specific compound, much less its *S*-isomer as an individual species. The instant compound, at best, is encompassed by the genus structure disclosed in Muller. *See, e.g.*, Muller, claim 1. Contrary to what the Examiner argues, the disclosure of this genus structure is not enough to render the use of the instant compound obvious. As discussed below, the Examiner's rationale is at odds with what Muller would have fairly suggested to one of ordinary skill in the art at the time of the invention, who does not have the benefit of hindsight. *See, e.g., In re Wesslau*, 353 F.2d 238,

341 (C.C.P.A. 1965) ("it is impermissible to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.").

First, the genus structure of Muller is broadly defined and encompasses thousands of compounds. To fully appreciate what would have been required to arrive at the instant compound, every step must be taken into account. To begin, Muller recites the following genus in claim 1:



The structure of the instant compound is:



Thus, to arrive at the instant enantiomer, one skilled in the art would have had to take the following steps:

(1) select CH_2 for **Y** from a list of C=O, CH_2, and CH_2C=O;

(2) select $-NR^8R^9$ for $\mathbf{R^1}$ from a list of hydrogen, halo, alkyl of 1-4 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, $-NR^8R^9$, or, taken together with an adjacent R^2, R^3, or R^4, naphthylidene;

(3) select H for $\mathbf{R^2}$ from a list of hydrogen, halo, alkyl of 1-4 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, $-NR^8R^9$, or, taken together with an adjacent R^1, R^3, or R^4, naphthylidene;

(4) select H for **R^3** from a list of hydrogen, halo, alkyl of 1-4 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, $-NR^8R^9$, or, taken together with an adjacent R^1, R^2, or R^4, naphthylidene;

(5) select H for **R^4** from a list of hydrogen, halo, alkyl of 1-4 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, $-NR^8R^9$, or, taken together with an adjacent R^1, R^2, or R^3, naphthylidene;

(6) select alkoxy of one carbon for **R^5** from a list of hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cyano, or cycloalkoxy of up to 18 carbon atoms;

(7) select alkoxy of two carbons for **R^6** from a list of hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cyano, or cycloalkoxy of up to 18 carbon atoms;

(8) select alkyl of 1 carbon for **R^7** from a list of hydroxy, alkyl of 1-8 carbon atoms, phenyl, benzyl, or $-NR^{8'}R^{9'}$, wherein each of $R^{8'}$ and $R^{9'}$ taken independently of the other is hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl, or one of $R^{8'}$ and $R^{9'}$ is hydrogen and the other is $-COR^{10'}$, or $-SO_2R^{10'}$, or $R^{8'}$ and $R^{9'}$ taken together are tetramethylene, pentamethylene, hexamethylene, or $-CH_2CH_2X^2CH_2CH_2-$ in which X^2 is –O–, –S– or –NH–;

(9) select H for **R^8** from a list of hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, benzyl, $-COR^{10}$, $-SO_2R^{10}$, or, taken together with R^9, tetramethylene, pentamethylene, hexamethylene, or $-CH_2CH_2X^1CH_2CH_2$, in which X^1 is –O–, –S– or –NH–;

(10) select COR^{10} for **R^9** from a list of hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, benzyl, $-COR^{10}$, $-SO_2R^{10}$, or, taken together with R^8, tetramethylene, pentamethylene, hexamethylene, or $-CH_2CH_2X^1CH_2CH_2$, in which X^1 is –O–, –S– or –NH–;

(11) select cyclopropyl for **R^{10}** from a list of alkyl of 1 to 8 carbon atoms or phenyl; and

(12) select the (S) isomer.

Yet Muller does not provide any teaching that suggests the desirability of performing any of the steps above. Because of this, one skilled in the art at the time of the invention – who does not have the benefit of hindsight – would not have had any reason to focus on the instant compound and, thus, would not have found the subject matter of the instant claims obvious. *See, e.g., In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994) ("[w]hile the [prior art

genus] unquestionably encompasses [the claimed compound] when specific variables are chosen, there is nothing in the disclosure of the [prior art] suggesting that one should select such variables."); *see also Takeda Chemical Industries, Ltd. v. Alphapharm Pty.*, Ltd. 492 F.3d 1350, 1359 (Fed. Cir. 2007) (claims held non-obvious in part because "[r]ather than identify predictable solutions...the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation."); *In re Deuel*, 51 F.3d 1552, 1558-9 (Fed. Cir. 1995) ("[n]o particular one of these DNA's can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared.") (emphasis added); MPEP §2144.08.

Further, with respect to the step of selecting the (S)-isomer, the Federal Circuit has addressed the issue of whether a single enantiomer of a compound can be nonobvious in view of a prior art disclosure of that compound's racemate and affirmed the patentability of chiral pharmaceutical compounds. *See, e.g., Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1090 (Fed. Cir. 2008); *Forest Labs., Inc. v. Ivax Pharmaceuticals, Inc.*, 501 F.3d 1263 (Fed. Cir. 2007); *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, 348 F.Supp.2d 713, 755 (N.D.W.Va. 2004). Whether a specific stereoisomer has improved biologically activity or a more desirable pharmacological profile is recognized as unpredictable in the art. *See e.g., Sanofi-Synthelabo* at 550 F.3d at 1090; *In re May,* 574 F.2d at 1092; *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F.Supp2d at 754 (the prior art suggested unpredictability in the degree of activity exhibited by a specific enantiomer). Here, the case for patentability is even stronger as the racemate itself is not even disclosed by the cited reference.

Muller does not disclose or suggest the (S)-isomer recited in the instant claims or its racemate. Indeed, Muller provides no preference for the biological or pharmacological activity of the specific racemic compound, much less any indication of the activity of the specifically claimed (S)-isomer for treating macular degeneration. Without specific guidance in the cited art, one of ordinary skill in the art would not have had any reason to select the specific (S)-isomer recited in the instant claims, and a *prima facie* case of obviousness cannot be made. *Takeda,* 429 F.3d at 1359. Thus, even assuming, *arguendo*, that one of ordinary skill in the art would have selected the racemate of the recited compound, Applicant respectfully submits that the instant claims, which specifically recite the (S)-isomer for treating macular degeneration, are not obvious by Muller.

Next, as discussed, the instant compound is not disclosed as an individual species in Muller. Rather, twenty other compounds are disclosed as individual species. *See, e.g.*, Muller, Examples 1-20. At best, a person skilled in the art would have focused on these specifically disclosed compound species, especially since full synthetic procedures and characterization data are provided for these species.[2] Rather than pursue the instant compound, which is not even clearly encompassed by the genus disclosed in Muller, one skilled in the art reading Muller at the time of the invention would more likely have pursued the twenty specifically disclosed species. *See, e.g.*, *Takeda*, 492 F.3d at 1360; *Yamanouchi Pharmaceutical Co. Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1344-45 (Fed. Cir. 2000) (selection of a compound not obvious because of known better alternatives).

It is also noted that the instant compound has a cyclopropylcarboxamide substituent. Yet not one of the twenty species disclosed in Muller have a cyclopropylcarboxamide substituent. Those skilled in the art at the time of the invention, upon studying the structures of these species, would have been led away from a cyclopropylcarboxamide substituent, and thus, would have been led away from the instant compound. In other words, Muller actually teaches away from the instant compound.

In sum, the mere fact that the instant compound may be encompassed by the genus of Muller is not enough to render the instant claims obvious. Holding otherwise is inconsistent with the realities of the research process and what Muller would have fairly suggested to a person of ordinary skill in the art at the time of the invention. This is especially true in the instant case because (1) the genus disclosed in Muller is broadly defined and encompasses thousands of compounds; (2) the instant compound is not specifically disclosed or suggested; (3) experimentals and characterization data are provided for twenty other compounds, leading to those as the ones obvious to try; and (4) Muller teaches away from a cyclopropylcarboxamide substituent. Faced with such a broadly-defined genus, a person skilled in the art would not have committed research efforts and expense on the instant compound absent any specific teaching. No such teaching has been provided by the Examiner.

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[2] Applicant does not concede that the selection of any of these species for the treatment of a disease is obvious. Rather, Applicant submits that such species were more likely to be pursued by a person of ordinary skilled in the art than the instant compound.

Tobinick and D'Amato do not cure the defects of Muller because nothing in these references would have given any reason to specifically select variable values for Y and R^1-R^{10} required to arrive at the instant compound from the large number of possibilities. Indeed, Tobinick teaches away from the recited compound by focusing on antibodies, not a small molecules as in the instant claims. Furthermore, nothing in Tobinick or D'Amato would have provided any insight as to the desirability of specifically isolating the (S)-isomer.

Even assuming, *arguendo*, that Muller does teach or suggest that the instant compound is a TNFα inhibitor, nothing in the cited references would have provided a reason to specifically single out macular degeneration. While the Examiner has alleged on page 3 of the Office Action that Tobinick "teaches the use of TNF alpha blockers or antagonists for the treatment of...macular degeneration," a broad genus of TNF-related disorders is disclosed. For example, Tobinick notes that "[t]hese disorders are diverse" and include among others:

> inflammatory and autoimmune disorders of the nervous system, including multiple sclerosis, Guillain Barre syndrome, and myasthenia gravis; degenerative disorders of the nervous system, including Alzheimer's disease, Parkinson's disease and Huntington's disease; disorders of related systems of the retina and of muscle, including optic neuritis, macular degeneration, diabetic retinopathy, dermatomyositis, amyotrophic lateral sclerosis, and muscular dystrophy; and injuries to the nervous system, including traumatic brain injury, acute spinal cord injury, and stroke.

Tobinick, column 2, lines 29-39. Yet the Examiner has failed to explain how Tobinick, Muller, or D'Amato would have provided a reason to single out macular degeneration from these disorders.

In sum, to arrive at the instant claims, a person of ordinary skill in the art would have had to take the following steps:

(1) select the proper values for Y and R^1-R^9 from the large number of possible values for the genus recited in claim 1 in Muller;

(2) select cyclopropyl for R^{10};

(3) specifically select the (S)-isomer; and

(4) specifically select macular degeneration from the large list of disorders disclosed in Tobinick.

However, as discussed, the Examiner has not pointed to any portion in the cited references that would have hinted the desirability of performing any of these steps. It is thus, only through hindsight, that the Examiner was able to piece together all the limitations of the instant claims. Those skilled in the art at the time of the invention, who do not have the benefit of hindsight, would not have had any reason to carry out the steps to arrive at the instant claims. Since such a reason is legally required for establishing a *prima facie* case of obviousness, the Examiner's rejection should be withdrawn.[3]

Finally, the Examiner has failed to explain how one skilled in the art would have had a reasonable expectation that the claimed compound would be effective in treating macular degeneration. The Federal Circuit, following *KSR*, articulated guidelines for determining "whether the expectation of success from a particular line of inquiry is great enough to render a resulting invention obvious." *PharmaStem*, 491 F.3d at 1364. As the Federal Circuit explained:

> [A]n invention would not be invalid for obviousness if the inventor would have been motivated to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. Likewise, an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Id., citing *In re O'Farrell*, 953 F.2d 894, 903 (Fed. Cir. 1988) (internal quotations omitted) (emphasis added).

In the instant case, to arrive at the instant compounds, not only would one skilled in the art have had to "try each of numerous possible choices" of variables from the genus of Muller, but one skilled in the art would also have had to "try each of numerous possible choices" of TNF-related disorders from Tobinick. Yet none of the cited references would have provided any "indication of which parameters were critical" or any "direction as to which of [the] many possible choices is likely to be successful." As is evident from *PharmaStem*, this scenario is exactly what the Federal Circuit warned is not a legally

[3] Claims 2-5 recite the use of the instant compound in combination with a second active component. Since Applicant has shown that a *prima facie* case of obviousness has not been established with respect to the claims reciting the use of the claimed compound, a *prima facie* case of obviousness with respect to claims 2-5 has also not been established.

sufficient "reasonable expectation of success." *Id.* The combination of references, at most, would have merely provided general guidance. Put in another way, the combination of references would have merely provided a list of many disorders and many compounds – yet would not have provided any indication as to why the instant compound would be specifically useful for the claimed disorder. Thus, the cited references do not provide the requisite expectation of success, and the rejection should be withdrawn.

B. Even if a *prima facie* case has been established, sufficient unexpected results are provided to overcome any *prima facie* case of obviousness

Even if a *prima facie* case of obviousness is established, the Examiner is required to consider all rebuttal evidence submitted by an applicant. *See In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007); *see also* MPEP §2145. This requirement remains unchanged following the decision in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), as the Federal Circuit has made clear in *In re Sullivan*. 498 F.3d at 1351. "When a patent applicant puts forth rebuttal evidence, the Board must consider that evidence." *Id.* Such rebuttal evidence includes "evidence of unexpected results." *Id.*, citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007).

In Applicant's Response filed October 15, 2008, Applicant submitted a declaration from Peter H. Schafer, Ph.D. ("Declaration")[4], which describes experiments that were performed to evaluate the *in vivo* activity of the instant compound in the treatment of macular degeneration. At the interview held on February 18, 2009, Applicant discussed unexpected results of the claimed invention.

As explained in the Declaration, the oral administration of the instant compound to mice unexpectedly resulted in remarkably higher inhibition of laser-induced choroidal neovascularization compared to the intravitreal injection of Lucentis®, which is a FDA-approved drug for the treatment of wet age-related macular degeneration.[5] *See, e.g.*, Declaration, paragraph 13 and Figure 1. Further, the oral administration of the instant compound to rats resulted in similar inhibition of laser-induced choroidal neovascularization

[4] Attached hereto as **Exhibit A**.

[5] Administration of the instant compound at 5 mg/kg BID resulted in a 69% reduction in the neovascular area, and the administration at 15 mg/kg resulted in 73% reduction in the neovascular area ($P<0.002$). The inhibition resulting from the intravitreal injection of Lucentis® was 36% ($P=0.0913$ under Dunnett's Method; $P=0.0423$ under Student's t-test).

compared to intravitreal injection of Lucentis®.[6] *See, e.g.*, Declaration, paragraph 14 and Figure 2. Thus, Applicant respectfully submits that these data represent sufficient unexpected results that rebut any alleged *prima facie* case of obviousness.

The Examiner alleges that the submitted data "are not commensurate in scope with the claim language." Office Action, page 4. It appears that the Examiner bases this allegation on three grounds. First, the Examiner alleges that "[the] data are done at 3 concentrations of the claimed compound by oral administration; however the claimed language is not limited to any concentrations or oral administration."[7] *Id.*

Applicant is not required to establish unexpected results with respect to every possible route of administration or every possible concentration. The nonobviousness of a broader genus can be supported by evidence based on unexpected results derived from a narrower genus or species as long as "one of ordinary skill in the art would be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof." *In re Kollman*, 595 F.2d 48, 201 USPQ 193 (CCPA 1979); *see also* MPEP §716.02(d). In this respect, Applicant points out that the instant claims are directed to the use of a compound for macular degeneration. The submitted data evidences the efficacy of the instant compound for the treatment of macular degeneration. On the basis of the observed efficacy, one skilled in the art would be able to "determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof" with respect to the scope of the instant claims.

Second, the Examiner alleges that "the comparative data are not done at the equal concentration for the claimed compound and Lucentis®." Office Action, page 4. However, since the instant compound and Lucentis® were administered using different routes of administration, it is unclear to Applicant why data showing efficacy at the same dosages should be required or is even relevant. The Examiner's focus should be on the fact that the instant compound was found to have comparable efficacy to Lucentis®, which is approved by the FDA and is considered to be the gold standard for treatment of macular degeneration.

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[6] Administration of the instant compound at 10 mg/kg BID resulted in a 61% reduction in the neovascular area, and administration at 25 mg/kg BID resulted in 65% reduction ($P<0.0001$). The inhibition resulting from the intravitreal injection of Lucentis® was 62% ($P<0.0001$).

[7] Four concentrations are provided: 5 mg/kg and 15 mg/kg for mice and 10 mg/kg and 25 mg/kg in rats.

Third, the Examiner alleges that "the data show the effect of the claimed compound on neovascularization; however the claims of the instant application are drawn to a method of treating macular degeneration. No correlation has been established between the treatment of choroidal neovascularization and the treatment of macular degeneration." Office Action, page 4. However, contrary to the Examiner's allegation, such correlation is established in the specification. For example, page 2 of the specification states: "Choroidal neovascularization is a problem...that is most commonly associated with MD." This correlation is recognized to those of ordinary skill in the art. *See, e.g.*, Campchiaro *et al.*, *Mol. Vis.*, 1999; 5: 34 ("Choroidal neovascularization (CNV) is the major cause of severe vision loss in patients with age-related macular degeneration....").[8]

In sum, the evidence presented in the Declaration are commensurate in scope with the instant claims and are sufficient to rebut any presumption of obviousness. Thus, the rejection under 35 U.S.C. §103 should be withdrawn.

Conclusion

A fee of $130.00 is believed due for the one-month extension of time. If any additional fees are due for the submission of this paper or to avoid abandonment of this application, please charge them to Deposit Account No. 50-3013.

Respectfully submitted,

Date: **March 5, 2009**

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[8] Attached hereto as **Exhibit B**. Also attached herewith is an Information Disclosure Statement and a "List of References Cited" to memorialize the Examiner's consideration of Exhibit B.